**INTRODUCTION**

Metastatic tumors to lymph nodes form the main body of neck masses and cystic lesions in the adult patients. The primary malignancies often found in head and neck regions are breast, melanoma, lung, thyroid, or occult metastatic squamous cell carcinoma. That being said, benign primary neck lesions such as branchial cleft cyst, thyroglossal duct, etc., should be carefully differentiated from metastatic tumors. An overtreatment such as neck lymph node dissections, could result if these benign entities are misdiagnosed as a metastatic cystic squamous carcinoma.

In children, the majority of the neck masses and cystic lesions are benign in nature, most commonly developmental anomalies, followed by inflammatory response, and in rare cases malignant tumors.

**MAJOR DIAGNOSTIC CONSIDERATIONS**

- Cystic lesions include cystic metastatic squamous carcinoma to cervical lymph nodes, branchial cleft cysts, thyroglossal duct cysts, cystic hygromas (lymphangiomas), teratomas, dermoid cysts, and thymic cysts.

- Lymphomas include Hodgkin’s and non-Hodgkin’s lymphoma.

- Paraganglioma (carotid body tumor) can be seen throughout the body; its most frequent representation in the head and neck area is carotid body tumor at the bifurcation of the internal and external carotid arteries. The location of the tumor is an important hint for this entity (Figs. 5.1 and 5.2).

- Schwannoma located in the internal auditory canal is also called *acoustic neuroma*. Schwannoma can also be seen in any branch of the cervical nerves (Fig. 5.3).
**Fig. 5.1** Paraganglioma: small nests of uniform tumor cells in a rich vascular stroma.

**Fig. 5.2** High power of a paraganglioma displays irregular, large, hyperchromatic nuclei (neuroendocrine atypia), a typical feature of this lesion.
• Reactive changes within a cervical lymph node can generate a false-positive diagnosis (Figs. 5.4 and 5.5).
• Sarcoidosis may be observed within a cervical lymph node (Fig. 5.6).
• Metastatic thyroid carcinoma to neck lymph nodes or soft tissue may be an unexpected finding without a known history of thyroid cancer (Figs. 5.7 and 5.8).
• Metastatic squamous cell carcinoma to neck soft tissue may be an unexpected finding when there is no known history of a primary squamous cell carcinoma (Fig. 5.9).

WHAT SURGEONS NEED TO KNOW INTRAOPERATIVELY TO CHOOSE THE OPTIMAL IMMEDIATE SURGICAL MODALITY
• Determining the nature of the lesions (metastatic carcinoma, primary malignancy including lymphoma or congenital cysts) to plan/evaluate the extent of the surgery
• Evaluating lymph nodes to determine a metastatic or a primary disease. For a metastatic carcinoma, they may start obtaining biopsies from different sites, looking for the origin. If it is a lymphoid process, they need to know if the tissue is representative and sufficient for an additional hematopathology workup
• Determining if the margins are clear for a resection of a known tumor

Fig. 5.3 Schwannoma at low power shows an alterative pattern, hypercellular and hypocellular areas, and palisading arrays of nuclei (Verocay bodies).
Fig. 5.4 Plasmacytosis (false-positive) node: there is a space-occupying focus at the periphery (capsule) of the node. A metastatic tumor needs to be ruled out.

Fig. 5.5 High power demonstrates typical plasma cells without significant atypia in the worrisome focus in Fig. 5.4. Subsequent immunostains confirmed a reactive process.
Fig. 5.6 Sarcoidosis in a cervical lymph node: non-necrotizing confluent granulomata, highly suggestive of sarcoidosis. Additional tissue should be requested for culture, if available; and special stains (GMS and AFB) should be performed.

Fig. 5.7 Metastatic thyroid papillary carcinoma to soft tissue in the neck with no previous known history of thyroid carcinoma.
**Fig. 5.8** Higher power of the previous case shows typical cytology of thyroid papillary carcinoma.

**Fig. 5.9** Metastatic squamous cell carcinoma to the skeletal muscle in the neck, with no known primary.
• Any perineural invasion, so the surgeon can decide to sacrifice a particular nerve branch. A conservative approach is to limit the procedure and wait for the final result from permanent sections

**SPECIMEN HANDLING AND GROSS DIAGNOSIS**

• Gross appearance of a branchial cleft cyst is usually unilocular with a central cavity. The cyst is lined by relatively thin and smooth inner wall. Solid areas can occasionally be seen due to inflammatory and reactive response to rupture of the cyst.
• Orientation with the help of the surgeon is critical before the specimen is cut.
• A smear or touch preparation can be useful, especially for small biopsy material.
• For a lymph node, it is always a good idea to find out the clinical indications before submitting the whole tissue to frozen section.
• Neck dissection for nodal metastasis is a frequent specimen we encounter. Division of specimen into different levels by the surgeon should be encouraged for intraoperative consultation or permanent examination, since they know the details of the regional anatomy and procedure.

**USEFUL DIAGNOSTIC PEARLS**

**Histologic Features of Cystic Squamous Cell Carcinoma to the Neck Lymph Nodes**

If there is a history of primary squamous cell carcinoma, it would be a good practice to compare the primary tumor with the metastatic disease. However, if there is no known history, histologic evaluation of the cystic lymphoepithelial lesions would be a last resort to diagnose a metastatic squamous cell carcinoma. Cases with obvious carcinoma features including loss of polarity, frequent mitoses, and cellular anaplasia, would not be difficult to diagnose a metastatic squamous cell carcinoma (Figs. 5.10 and 5.11). Diagnosing cases of “low-grade” metastatic carcinoma at frozen section is challenging.

The majority of occult metastatic squamous cell carcinomas arise from the tonsillar area, and they usually show the following morphologic features (Fig. 5.12):

1. Large unilocular cyst with a thick fibrous capsule formation (occasionally multiple small cysts can be seen as well), predominately a cystic lesion with only focal areas of solid growth
2. Cystic spaces lined by a squamous or transitional epithelium arranged in strips of epithelium of relatively uniform thickness, with areas maintaining the surface maturation
3. No prominent degree of anaplasia; the cells recapitulate the normal tonsillar crypt epithelium
**Fig. 5.10** Solid sheets of squamous cell carcinoma at the subcapsular location with adjacent residual lymphoid tissue. This histology is most consistent with a known primary squamous cell carcinoma.

**Fig. 5.11** Central necrosis, tissue debris, and keratinization are often seen in a lymph node positive for metastatic squamous cell carcinoma.
4. With careful searching and necessary sectioning, atypia beyond a reactive change encountered in benign bronchial cysts will be found.

**Common Histologic Features of Benign Cervical Cysts**

1. The lining of a branchial cleft cyst is mostly composed of a simple keratinizing squamous epithelium. The occasional presence of ciliated pseudostratified respiratory epithelium can be a helpful histologic finding favoring a benign diagnosis. Atypia from a reactive response is a diagnostic pitfall to keep in mind (Figs. 5.13–5.15).

2. Thyroglossal duct often contains a portion of benign thyroid tissue. Benign keratinizing squamous lining can be seen as well. The central location differentiates it from the metastatic lymph node.

3. Hassall's corpuscles are found in thymic cysts.

4. Lymphangioma is lined by benign lymphatic endothelial cells.

5. Frozen sections are commonly requested for these benign cysts. The most important differential diagnosis is metastatic squamous cell carcinoma with cystic change.
Fig. 5.13  Benign cystic structure with lymphoid aggregates identified within a branchial cleft cyst. There is no significant cellular atypia.

Fig. 5.14  The lining of a branchial cleft cyst is a simple keratinizing squamous epithelium with epithelial maturation.
Fig. 5.15  Reactive atypia and pseudoinvasion within a branchial cleft cyst should not be confused with a metastatic squamous cell carcinoma.

- When markedly sclerosing fibrous bands are seen, the possibility of sclerosing nodular Hodgkin’s lymphoma should be ruled out before calling it reactive. A touch preparation can be useful to show the mixed cellularity and Reed–Sternberg cells (Figs. 5.16–5.18).
- Determination of specimen adequacy for special tests, such as cultures for a possible infectious process (granulomatous inflammation) (Fig. 5.19), personalized therapy protocol (molecular studies), or flow cytometry.
- Diagnostic (sufficient) fresh tissue is obtained from a lymphoproliferative process, so that additional studies such as immunohistochemistry, flow cytometry, cytogenetic, and molecular tests can be performed at a later time. If not comfortable that sufficient tissue has already been provided for these studies, additional tissue should be requested immediately. By doing this, we can avoid another surgical procedure to obtain the diagnostic tissue. If no immediate therapy will be implemented at the time of frozen section, saving the valuable tissue for a thorough investigation later is the best option at the time of the intraoperative consultation (Figs. 5.20 and 5.21).
**Fig. 5.16** Hodgkin’s lymphoma. Nodular and sclerosing pattern should remind us of a Hodgkin’s lymphoma.

**Fig. 5.17** Touch preparation of the above case shows typical Reed–Sternberg cells.
Fig. 5.18 Frozen section of the above case shows typical Reed–Sternberg cells.

Fig. 5.19 Necrotizing granuloma in a cervical lymph node: a diagnosis of “negative for malignancy” can be made. Additional tissue for microbiology culture should be requested; and special stains (GMS and AFB) will be performed on the permanent sections.
**Fig. 5.20** Diffuse large B-cell lymphoma. Touch preparation shows a diffuse process; the cells are large (compared to the lymphocytes) and are not cohesive.

**Fig. 5.21** Frozen section of the above case demonstrates discohesive tumor cells with necrosis and mitoses. Additional fresh tissue should be requested for additional tests.
COMMON DIAGNOSTIC PITFALLS

- A benign cyst with reactive atypia may be misdiagnosed as a well-differentiated metastatic squamous cell carcinoma.
- Reactive changes within a lymph node may generate a false-positive diagnosis and subsequently lead to numerous biopsies searching for primary neoplasm and/or a neck dissection.
- Thick fibrous bands within a sclerosing nodular Hodgkin’s lymphoma may be misinterpreted as a reactive process.
- It is better to defer a lymphoproliferative process to additional lymphoma workup, rather than struggle to reach an accurate diagnosis at the time of intraoperative consultation.